Guidance for Industry and Review Staff

Formal Dispute Resolution: Appeals Above the Division Level

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Guidance for Industry and Review Staff

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TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND 2

A. Regulatory Framework 2

B. Scope of the Guidance 3

III. REQUEST FOR FORMAL DISPUTE RESOLUTION 4

IV. PROCEDURES FOR SUBMITTING A REQUEST FOR FORMAL DISPUTE RESOLUTION 5

A. How to Request Formal Dispute Resolution 5

1. Requests for CDER 5

2. Requests for CBER 6

B. Supporting Background Information 6

V. FDA ACTION 7

A. Responses to an Appeal 7

1. Timelines for Reviewing Formal Dispute Resolution Requests for Human Drug Applications Covered by PDUFA 8

2. Timelines for Reviewing Formal Dispute Resolution Requests for Human Drug Applications not Covered by PDUFA 9

B. Additional Considerations Regarding Responses to Appeals That Request Advisory Committee Review 9

1. Granting of a Request for Advisory Committee Review 9

2. Denial of a Request for Advisory Committee Review 9

VI. REPEAT APPEALS 10

Guidance for Industry and Review Staff[1]
Formal Dispute Resolution:
Appeals Above the Division Level

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to provide recommendations for industry on the procedures in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) for resolving scientific and procedural disputes that cannot be resolved at the division level. This guidance describes procedures for formally appealing[2] such disputes to the office or center level and providing information to assist FDA officials in resolving the issue(s) presented.

In the course of drug review, CDER and CBER make a wide variety of scientific and procedural decisions that are critical to a sponsor's[3] drug development program.[4] Sometimes, a sponsor may disagree with one of these decisions, and a dispute arises. Because these disputes often involve complex scientific or procedural matters and also may be precedent setting, it is critical that there be procedures in place to encourage open, prompt discussion of such disputes. The procedures and policies described in this guidance are intended to promote rapid resolution of

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For purposes of this guidance, an *appeal* is a request for formal dispute resolution.

[3] For purposes of this guidance, the term *sponsor* includes any sponsor, applicant, or manufacturer of a new drug, generic drug, or biological product regulated by the FDA under the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act.

[4] For purposes of this guidance, a *drug* includes both human drugs and human biologics.

scientific and procedural disputes between sponsors and the Food and Drug Administration (FDA).[5]

This draft guidance is a revision of the guidance of the same name that issued in February 2000. When finalized, this guidance will replace the February 2000 guidance. This guidance is being revised to update procedures and policies to reflect current practice.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Regulatory Framework

Section 404 of the Food and Drug Administration Modernization Act of 1997 created new section 562 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360bbb-1). Section 562 of the FD&C Act provides that if, regarding an obligation concerning drugs or devices under the FD&C Act or section 351 of the Public Health Service Act, there is a scientific dispute between the FDA and a sponsor, applicant, or manufacturer, the FDA will, by regulation, establish a procedure under which such sponsor, applicant, or manufacturer may request a review of the controversy, including review by an advisory committee. Section 562 of the FD&C Act further provides that such review of the controversy, if granted, will take place in a timely manner.

FDA regulations (21 CFR 10.75) provide a mechanism for any interested person[6] to obtain formal review of any FDA decision by raising the matter with the supervisor of the employee who made the decision. If the issue is not resolved at the primary management (i.e., division) level, the interested person may request that the matter be reviewed at the next higher management level. This process may continue through the FDA's chain of command (i.e., through the centers to the FDA Commissioner of Food and Drugs). Regulations for dispute

[5] This guidance does not apply to purely internal disputes involving FDA staff. Additionally, this guidance is not intended to address the alternate dispute resolution pathway of appealing a dispute to the Drug Safety Oversight Board that exists for risk evaluation and mitigation strategies modified or required after initial approval of the drug (21 USC 355-1(h)(5)). For guidance on how to resolve disputes of scientific and technical issues relating to current good manufacturing practice requirements, see the guidance for industry *Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[6] For purposes of this guidance, the term *interested person* is a person who submits a petition, comment, or objection or otherwise asks to participate in an informal or formal administrative proceeding or court action (21 CFR 10.3). This definition of interested person includes a sponsor, applicant, or manufacturer of a drug or biological product, but does not include FDA staff.

resolution during the investigational new drug application (IND) process (21 CFR 312.48) and the new drug application (NDA)/abbreviated new drug application (ANDA) process (21 CFR 314.103) specifically establish procedures for the resolution of scientific and procedural matters at the division level and subsequent formal review of decisions through center management. CDER and CBER regulations also provide that a sponsor may ask the FDA to seek the advice of outside experts, including an appropriate advisory committee, in resolving the matter (§§ 312.48(c)(3) and 314.103(c)(3)).

In the *Federal Register* of November 18, 1998 (63 FR 63978), the FDA amended § 10.75 to explicitly state that a sponsor, applicant, or manufacturer of a drug or device may request review of a scientific controversy by an appropriate advisory committee. In the preamble to the final rule, the FDA stated that implementation of this provision would be undertaken by the individual FDA centers and would be described in guidances. The guidance for industry published in February 2000 met that commitment.

B. Scope of the Guidance

In the Prescription Drug User Fee Act of 1992 (PDUFA) and subsequent reauthorizations,[7] the FDA agreed to specific performance goals for activities associated with the development and review of human drug applications as defined in section 735(1) of the FD&C Act (21 U.S.C. 379g(1)). These performance goals contain specific time frames for resolving disputes affecting an IND, NDA, or biologics license application (BLA). For disputes involving human drug applications covered by PDUFA, the PDUFA goal is to respond to an appeal of a dispute above the original signatory authority within 30 calendar days of the center's receipt of the written appeal (see section V.A.1., Timelines for Reviewing Formal Dispute Resolution Requests for Human Drug Applications Covered by PDUFA).

In the Generic Drug User Fee Act, the FDA agreed to specific performance goals for generic drugs.[8] The goals state, "[f]or appeals of decisions concerning procedural or scientific matter involving review of pending ANDAs, ANDA amendments and ANDA supplements, FDA will aspire that the response to appeals of decisions will occur within 30 calendar days of [Office of Generic Drugs] receipt of the written appeal when possible, though no reportable performance goals are required." *Id.* The procedures described in this guidance generally will be applied and the time frames will be met when possible (see section V.A.2., Timelines for Reviewing Formal Dispute Resolution Requests for Human Drug Applications not Covered by PDUFA).

[7] See letters from the Secretary of Health and Human Services to the Chairman of the Committee on Health, Education, Labor, and Pensions of the Senate and the Chairman of the Committee on Energy and Commerce of the House of Representatives, as set forth in the Congressional Record (http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm149212.htm) and Section A: PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017 (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf).

[8] Generic Drug User Fee Act Program Performance Goals and Procedures (http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf)

Similarly, for CBER-regulated drugs and CBER-regulated medical devices (covered by the Medical Device User Fee Act), the procedures described in this guidance generally will be applied and the time frames will be met as resources permit (see section V.A.2., Timelines for Reviewing Formal Dispute Resolution Requests for Human Drug Applications not Covered by PDUFA).

A sponsor may choose not to follow the formal dispute resolution process and may informally raise a procedural or administrative matter with the CDER or CBER Ombudsman (§§ 312.48 and 314.103).[9] In addition, a sponsor who has sought formal dispute resolution and remains dissatisfied after a decision has been made may also seek the assistance of the CDER or CBER Ombudsman in facilitating resolution of the matter. The procedures described in this guidance do not apply to such informal dispute resolution through the CDER or CBER Ombudsman. Such informal contacts with the Ombudsman concerning human drug applications are not subject to user fee goals. It is important to note that although sponsors can seek advice from the Ombudsman at any time, they are encouraged to pursue an appeal either informally or formally, but not informally and formally at the same time.

III. REQUEST FOR FORMAL DISPUTE RESOLUTION

As described in FDA regulations (§§ 10.75, 312.48, and 314.103), when a dispute arises, the sponsor should initially seek resolution of any scientific or procedural dispute at the division level before making an appeal to the next higher management level. Sponsors can do this by holding a post-action meeting with the division or asking the division for reconsideration. For example, if there is a dispute regarding a deficiency cited in a complete response letter, the sponsor should first request a post-action meeting with the division to discuss the issue. Or, if an IND has been put on clinical hold, the sponsor should first ask the division to reconsider the issue.

Because all FDA decisions on any dispute must be based on information already in the relevant administrative file (§ 10.75(d)), no new information should be submitted as part of a request for reconsideration or appeal. If the sponsor has new information that may affect the original decision, any appeal should be deferred until the new information has been submitted to the administrative file and reviewed by the division. New analyses of data previously reviewed should be considered new information, and therefore should be submitted to the division for review before being submitted as support for an appeal.

[9] For more information on the CDER or CBER Ombudsman, see the following Web sites, respectively: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ContactCDER/CDEROmbudsman/default.htm and http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm122881.htm.

A sponsor should wait to submit an appeal until after the pertinent information has been reviewed at the division level. For example, if a meeting is scheduled between a sponsor and a division to discuss an issue, and at the same time the sponsor submits a formal dispute resolution request appealing the same issue, the FDA will not consider the appeal because the issue is still under review at the division level. In addition, the FDA will not consider an appeal if information that has not been previously reviewed by the division has been submitted in support of the appeal.

A sponsor may request a Type A meeting as part of its appeal.[10] This meeting is an opportunity for the sponsor to discuss the appeal issue(s) with the reviewing official.[11] If a sponsor is requesting such a meeting, the sponsor should indicate such request in the written request for formal dispute resolution.

Additionally, a sponsor can request that a scientific dispute be reviewed by an appropriate advisory committee as part of an original formal appeal or at any point in the formal dispute resolution process by submitting the request for advisory committee review as an amendment to the formal appeal. Because it can take a significant amount of time to schedule an advisory committee meeting, if a sponsor believes that review by an advisory committee is the most appropriate venue for resolution of a scientific controversy, such a request should be made as early in the dispute resolution process as feasible.

IV. PROCEDURES FOR SUBMITTING A REQUEST FOR FORMAL DISPUTE RESOLUTION

A. How to Request Formal Dispute Resolution

The sponsor should submit a written request with a complete background package to the appropriate CDER or CBER organization as described below. *Before submitting a request, it is strongly encouraged that sponsors contact the appropriate center and provide advance notice of the pending submission to ensure prompt handling of the appeal. Contact information is provided below.*

1. Requests for CDER

Requests for formal dispute resolution with CDER, should be submitted to the sponsor's application (e.g., IND, NDA, BLA, ANDA). The request should be submitted as an amendment to the application to the appropriate review division, and a copy should be submitted to the CDER Formal Dispute Resolution Project Manager (FDRPM). The contact information can be

[10] See the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[11] For purposes of this guidance, the term *reviewing official* refers to the person assigned to make the decision on the appeal.

found on the CDER Contact Information Web site.[12] We encourage sponsors to contact the FDRPM before submitting a request for formal dispute resolution.

2. Requests for CBER

Requests for formal dispute resolution with CBER should be submitted to the CBER Ombudsman. The contact information can be found on the CBER Ombudsman Web site.[13] We encourage sponsors to contact the CBER Ombudsman before submitting a request for formal dispute resolution. Note that the CBER Ombudsman handles both informal and formal dispute resolution requests, so the decision to use the formal route should be clear in the submission.

B. Supporting Background Information

To make the most efficient use of FDA and industry resources, any request for formal dispute resolution to either CBER or CDER should include information adequate to explain the nature of the dispute and to allow the FDA to determine the necessary steps needed to resolve the matter quickly and efficiently. Each request should include the following:

- Identification of the submission as FORMAL DISPUTE RESOLUTION REQUEST in bold, uppercase letters.
- The application number (e.g., IND, NDA, BLA, ANDA),[14] if applicable.
- The proprietary and/or generic name and established name for drug products; proper name and trade name for biological products.
- The division or office where the application is filed.
- The proposed indication(s), if applicable.
- A brief, but *comprehensive* statement of each issue to be resolved, including:
  - A description of the issue to be resolved
  - Identification of the issue as scientific, procedural, or both
  - A statement of the steps that have been taken to resolve the issue, including any previous informal and formal dispute resolutions

[12] See http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ContactCDER/CDEROmbudsman/ucm278559.htm.

[13] See http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm122881.htm.

[14] If the request is related to a CBER-regulated device, the request should include the application number (e.g., investigational device application, 510(k), premarket approval application, BLA).

  - Identification of possible solutions, including, for scientific issues, whether an advisory committee review is requested

  - A statement of whether a Type A meeting is requested

  - A statement of the proposed outcome

- A statement identifying the division and/or office that issued the *original* decision on the matter and, if applicable, the last management level and official who attempted to formally resolve the matter.

- A list of documents previously submitted to the FDA that are deemed necessary for resolution of the issue(s), with reference to submission dates so the documents can be readily located. Copies of such documents can be resubmitted to the FDA as appendices to the request (if not too voluminous).

- A statement that the previous management level has received and had the opportunity to review all of the material relied on for dispute resolution.

- The name, title, and contact information (i.e., mailing address, email address, telephone number, fax number) for the sponsor contact for the appeal. If a sponsor decides that the contact for the appeal will be a third party, the sponsor should state that the third party has been granted permission to act on its behalf regarding the dispute.

V. FDA ACTION

The formal request should be reviewed and forwarded by the FDRPM or CBER Ombudsman, as appropriate, to the appropriate CDER or CBER management level, as established under the center chain of command. The FDA should send an acknowledgment letter to the sponsor identifying the reviewing official, the due date for response to the request for formal dispute resolution, and the date of the meeting (if applicable).

A. Responses to an Appeal

In general, the FDA will send a written decision to a sponsor who requests formal dispute resolution. The written decision will grant or deny the appeal, and respond to all components of the appeal. Specifically, the decision may agree or disagree with the entire proposed outcome desired by the sponsor, agree or disagree with parts of the proposed outcome, or suggest a resolution that is different from that proposed by the sponsor. If the FDA does not agree with all or part of the sponsor's position, the decision should provide the reasons for the disagreement and identify any actions that the sponsor can take to address issues the FDA has raised. The FDA may also provide an interim response, such as a request for additional clarifying information or a request for a meeting with the sponsor, before making a decision on the appeal.

1. Timelines for Reviewing Formal Dispute Resolution Requests for Human Drug Applications Covered by PDUFA

If a procedural or scientific dispute concerns a human drug application covered by PDUFA, the FDA should complete the review and provide a decision on the appeal within 30 calendar days from receipt of the appeal. The FDA should respond to the sponsor within the 30-day window in writing or by telephone (i.e., *30-day response*). If the response is by telephone, the FDA should follow up with a written confirmation within 14 calendar days of the verbal response.

If a sponsor requests a meeting as part of its appeal, the meeting request should be treated as a Type A meeting. Under the PDUFA meeting goals, the FDA should either grant or deny the meeting request within 14 calendar days of receipt of the appeal. If the meeting is granted, the FDA has 30 calendar days after the meeting date to provide a decision on the appeal. This time period allows the FDA to consider the discussion at the meeting in its decision making process.

There may be instances where the FDA needs additional clarifying information or input from other persons knowledgeable in the matter to reach a decision. If the drug is a human drug application covered by PDUFA, such *interim responses* should be made within 30 calendar days of receipt of the appeal.

- In instances where the FDA needs additional clarifying information from the sponsor (note: this does not mean new information that has not been reviewed by the division), a request for this information should be sent within 30 calendar days from receipt of the appeal. The FDA should render a decision on the appeal within 30 calendar days from receipt of the information to the administrative file.

- In instances where the FDA decides a meeting with the sponsor is needed before a response can be issued, a meeting request should be sent within 30 calendar days from receipt of the appeal. The FDA should schedule such meetings as quickly as the sponsor and the FDA are able to agree on a mutually acceptable date and time. After the meeting is held, the FDA should render a decision on the appeal within 30 calendar days from the meeting date.

- In instances when the FDA requires limited discussion with one or more members of an advisory committee or internal or external experts, the FDA should inform the sponsor of this plan within 30 calendar days from receipt of the appeal. The FDA should schedule such limited discussions as quickly as all parties are able to agree on a mutually acceptable date and time. After this limited discussion is held, the FDA should render a decision on the appeal within 30 calendar days from the date of the discussion.

- Additionally, there are instances where the FDA may request an advisory committee review. If the drug is a human drug application covered by PDUFA, the FDA should inform the sponsor of this plan within 30 calendar days from receipt of the appeal. The FDA should render a decision on the appeal within 30 calendar days after the date of the advisory committee meeting.

If the FDA is unable to complete the review and provide either an interim response or a decision on the appeal within 30 calendar days, the FDA should notify the sponsor, explain the reasons for the delay, and discuss the time frame for completing the review. In these cases, the PDUFA goal for the appeal response would not be met.

2. Timelines for Reviewing Formal Dispute Resolution Requests for Human Drug Applications not Covered by PDUFA

If the matter under appeal does not pertain to a human drug application covered by PDUFA, the FDA should make all reasonable efforts to resolve the dispute as expeditiously as possible and should provide a written or telephone response to the sponsor in a timely manner. If the response is by telephone, the FDA should follow up with a written confirmation within 14 calendar days of the verbal notification.

B. Additional Considerations Regarding Responses to Appeals That Request Advisory Committee Review

If a sponsor seeking resolution of a scientific dispute requests advisory committee review of the matter, the FDA should determine whether such review is appropriate and helpful to the FDA at that time in the formal appeal process. The FDA should communicate this determination to the sponsor following the procedures described in section V.A., Responses to an Appeal.

1. Granting of a Request for Advisory Committee Review

If the request for review by an advisory committee is granted, the matter should be brought to the next scheduled advisory committee meeting for which there is time available on the agenda for adequate discussion of the issue. Because of administrative concerns related to organizing each advisory committee meeting (e.g., establishing an agenda, sending background information to the advisory committee members before the meeting), it may not be feasible to raise the matter at the next scheduled meeting.

As discussed in FDA regulations (21 CFR 14.5(b)) and the preamble to the final rule amending § 10.75, the advice and recommendations of an advisory committee after review of a scientific dispute do not bind the FDA to a particular action or policy. After receiving the advice of the appropriate advisory committee, the FDA should notify the sponsor of its determination on the matter within 30 calendar days.

2. Denial of a Request for Advisory Committee Review

If the FDA does not grant the request for advisory committee review, the FDA should notify the sponsor in writing of such decision, including the reason(s) for the denial and any steps the sponsor may take to persuade the FDA to reverse its decision.

VI. REPEAT APPEALS

If a sponsor's appeal is denied at one management level, the sponsor can appeal the same issue to the next higher management level in the chain of command in the center. After exhausting the center's management levels, a sponsor can request review of the center's decision by the FDA Commissioner of Food and Drugs. As stated in § 10.75, requests for such review should be submitted to the FDA's Ombudsman.[15] Each appeal to each management level should follow the process provided in this guidance. If a sponsor is appealing to the FDA Commissioner, copies of the appeal should also be sent to the centers as described in section IV.A., How to Request Formal Dispute Resolution.

[15] See the FDA's Office of the Ombudsman Web site at http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/ucm197508.htm.